REMARKS

A. The objection to the specification has been overcome

The Examiner objected to the amendment to the paragraph beginning at page 4, line 26, asserting that incorporation of the names of the 46 non-essential genes of herpes simplex virus was an improper incorporation by reference of essential matter. The Examiner further asserted that "the new material added to the specification is 'essential material' . . . ." Office Action at page 3.

The current Office Action essentially repeats the objection from the previous Office Action, with some elaboration. Reconsideration of the objection is requested in view of Applicants' previous response and the response provided herein. It is respectfully submitted that the basis for the objection to the specification under 35 U.S.C. § 232 for new matter was overcome by Applicants' previous response, which the Examiner appears to have misunderstood. In particular, the Examiner asserts that Applicants' argument has been that the amendment is not new matter because the specification indicates that the Roizman article (PNAS 1996) has been incorporated by reference. Office Action at page 2. Continuing, the Examiner again reminded Applicants of MPEP § 608.01(p). Office Action at pages 2-3. The only additional reasoning provided in support of the objection is that "the material which has been added to the specification is considered 'essential material' because it is necessary to describe the claimed invention. . . .Since the new material added to the specification is 'essential material' it may not be incorporated by reference . . . ." Office Action at page 3.

The Examiner's characterization of Applicants' argument as relying on the mere act of incorporating matter by reference to overcome the new matter objection, and the repeated reminder regarding MPEP § 608.01(p), reveal that the Examiner has misunderstood Applicants' position. Applicants have not argued that the incorporation by reference of disclosures in Roizman 1996 obviates the new matter objection. Applicants are aware that incorporated matter may be either essential or non-essential, and that essential matter may only be incorporated in accordance with MPEP § 608.01(p). Thus, Applicants have not argued that the mere act of incorporating by reference establishes that the incorporated material is non-essential.

Applicants' argument has been, and continues to be, that the matter incorporated from Roizman 1996 is not essential matter because it is the mere addition of a synonym for a phrase originally recited in the specification. That originally recited phrase, "one or more of the 47 genes found dispensable for viral replication in culture," identifies the complete collection of non-essential HSV genes. Applicants are merely amending the specification to provide an alternative way of defining that complete collection of non-essential HSV genes, as defined in the cited Roizman 1996 publication. The Examiner's criticism of the Roizman reference in the previous Office Action, moreover, does not change that fact.

Table 1 of the Roizman reference individually identifies each of the 84 total distinct genes of HSV and specifically identifies each of the 46 non-essential genes of HSV in an unambiguous manner. See, e.g., column 3 of Table 1, which identifies each non-essential gene with a "Y" and each essential gene with an "N." Consistent with this disclosure is Fig. 1 of that reference, which identifies the total number of single copy genes as 84. In the right column of page 11309, Roizman explains that there are five ORFs that are present in two copies each, accounting for the remainder of the 89 total genes identified in Figure 1. Additional disclosure in Roizman corroborating these gene identifications is the passage at page 11309 (left column) that there are 84 different polypeptides encoded by ORFs distributed as indicated in Fig. 1.

The Examiner, however, has pointed to a passage at page 11310, left column, first full paragraph, where it is effectively recited that 45 of the 83 genes of HSV are non-essential. In that same paragraph, there is a statement that the 45 accessory ORFs are not required for viral replication in cells in culture. That same paragraph also states that "[a] list of the ORFs and the functions expressed by the gene products are shown in Table 1." As noted above, Table 1 identifies 46 non-essential genes, not 45, and Table 1 identifies 84 total unique genes, not 83.

One of skill in the art, reviewing the entire disclosure of the Roizman reference, would note that Fig. 1 identifies 84 total single-copy genes, that page 11309 corroborates the identification of 84 total unique genes, and that Table 1 explicitly sets forth

and identifies each of the 84 total unique genes as well as identifying 46 of those 84 genes as non-essential for viral replication in cells in culture. The statement at page 11310 that there are 83 genes, with 45 of those 83 genes being non-essential genes, is made in the context of relying on the disclosures of Table 1. Thus, the passage at page 11310 would be seen by one of skill in the art as inadvertently underreporting the total number of genes and the number of non-essential genes of HSV set forth in Table 1, with each being underreported by a single gene. One of skill in the art would conclude that the passage at page 11310 reflected typographical errors in the number of non-essential and total genes of HSV. Moreover, the Examiner has not cited any publication, appearing before or after the Roizman 1996 publication, that is inconsistent with this identification of 84 total HSV genes and 46 non-essential HSV genes.

For the foregoing reasons, Applicants submit that Roizman 1996 does provide the disclosure of 46 non-essential HSV genes. The Examiner identified as assertedly new matter the naming of the 46 nonessential genes of HSV. Applicants submit that the assertedly new matter is merely the names of the 46 nonessential genes of HSV. The application-as-filed expressly stated that viruses could be further attenuated by deletion of one or more of the genes found dispensable for viral replication in culture. One of skill in the art would understand that an HSV gene dispensable for viral replication in culture is a nonessential HSV gene. Therefore, the original application described the invention as including viruses lacking one or more nonessential genes of HSV. That is not new matter, and Applicants acknowledge that the Examiner has not asserted otherwise. At issue, then, is whether the names of the nonessential genes is new matter that is essential to the claimed subject matter. The 1996 Roizman reference cited in the relevant passage of the application-as-filed (*see* above), however, provides the names of those 46 nonessential genes of HSV, establishing that the names of the nonessential genes of HSV were well known in the art as of the February 5, 1999 priority date claimed in the instant application. The recitation of the names of all of the nonessential genes of HSV is synonymous with the recitation of those genes nonessential to HSV, merely providing an alternate form of identifying those genes, as would be understood by one of skill in the art. The question thus becomes whether the naming of each member of an identified group or genus, whose members are known in the art, is essential matter.

As defined in MPEP § 608.03(p)(c1-c3), essential material is defined as:

> material that is necessary to: (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112; (2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 U.S.C. 112; or (3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 U.S.C. 112.

Based on the above-quoted section of the MPEP, essential material is material required to (1) satisfy a requirement of 35 U.S.C. § 112, first paragraph, i.e., it must be required to provide adequate written descriptive support, to enable, to disclose best mode or to avoid indefinite claim language, or (2) satisfy the requirement of 35 U.S.C. § 112, second paragraph for definite claim language, or (3) satisfy the 35 U.S.C. § 112, sixth paragraph requirement for structures, materials or acts corresponding to claim-recited means. None of the claims-at-issue are means-plus-function claims and, hence, option (3) is not relevant here. As for option (2), there can be no difference in the definiteness of terms that are synonyms. By way of example, a reference to each and every element of the periodic table is no more or less indefinite than a collective reference to all of the elements of the periodic table, which are known in the art. Analogously, a claim recitation of the non-essential genes of HSV is synonymous with a claim recitation of the name of each and every one of those non-essential genes. Thus, the amendment to the specification adding the names of all non-essential genes of HSV is not an amendment adding essential material because of the requirement of 35 U.S.C. § 112, second paragraph.

Finally, none of the requirements of 35 U.S.C. § 112, first paragraph, lead to the conclusion that the above-referenced amendment adds essential material. First, the written description requirement is designed to ensure that one of skill would understand that

the inventors had possession of the claimed invention as of the effective filing date. A description of that invention using either of two synonymous terms, each known in the art, could not lead one of skill to conclude that the inventors had possession of the invention when that invention was described using one of the two synonyms (e.g., a non-essential HSV gene), but that such possession could not be acknowledged when the same invention was described using the second synonym (e.g., the actual names of all of those non-essential HSV genes). Analogously, there can be no lack of enablement peculiar to a claim reciting one of the two synonyms, and the Examiner has not contended otherwise. A disclosure teaching the making and using of an invention comprising a modified HSV further comprising a mutation in a non-essential gene is also a disclosure teaching the making and using of an invention comprising a modified HSV further comprising a mutation in any of the specifically identified non-essential HSV genes known in the art. Finally, the recitation of either of two synonymous terms cannot result in a failure to disclose any best mode contemplated by the inventors at the relevant time. Accordingly, the specific names of the non-essential HSV genes known in the art are not required to satisfy any of enumerated points (1)-(3) of MPEP § 608.03(p)(c1-c3) and, for that reason, an amendment adding those specific names to the specification does not involve the addition of essential material. Because the specific names of the non-essential HSV genes do not constitute essential material, the incorporation by reference from the Roizman publication is proper and the objection to the specification should be withdrawn.

B. The rejection of claims 1-5 for lack of written description has been overcome

The Examiner asserted that claims 1-5 were rejected under 35 U.S.C. § 112, first paragraph, for lack of written descriptive support and noted that this rejection was a "new matter rejection." In support, the Examiner relied on reasons of record, which were reiterated in the Office Action. The reiterated reason for the rejection was that claim 5 encompassed genes that were not disclosed in the originally filed specification. The Examiner further requested that Applicants identify, by page and line number, the location of support for non-essential HSV genes other than those expressly recited in the application as filed. Office Action at page 4. In response, Applicants traverse.

As an initial matter, Applicants request reconsideration of the rejections of claims 1-4 separate and apart from a consideration of the rejection of claim 5 on the instant ground. The Examiner's apparent issue is with the comprehensive, but assertedly unsupported, recitation of non-essential HSV genes found only in dependent claim 5. The assertedly unsupported subject matter is not recited in any of claims 1-4. None of claims 1-4 recites any of the assertedly new matter in the form of non-essential HSV genes lacking express, literal support in the specification, and none of claims 1-4 is missing an essential element. For this reason alone, the rejection of each of claims 1-4 under 35 U.S.C. § 112, first paragraph, is legally erroneous. It is completely irrelevant to the patentability of each of independent claims 1-4 whether a claim dependent thereon introduces a further limitation that does or does not satisfy the written descriptive requirement. The Examiner has erred as a matter of law and the rejection of each of claims 1-4 on the instant ground should be withdrawn.

The reiterated reason for rejecting claim 5 under § 112, first paragraph, for lack of written descriptive support is that claim 5 encompassed HSV genes not disclosed in the application as filed. Applicants note three observations in responding to the Examiner's position. First, the Examiner did acknowledge support for each non-essential HSV gene expressly disclosed in the application-as-filed. Office Action at page 4. Second, theExaminer did not acknowledge any support in the recitation of further attenuating the HSV according to the invention by deleting one or more HSV genes dispensable for culture or by the citation to the 1996 Roizman reference, which was incorporated by reference. (See page 5, lines 12-15.) *Id.* Third, the Examiner expressly requested citation to the specification wherein support for the "other" HSV genes could be found. Based on these three observations, it is apparent that the Examiner has applied an improper standard in assessing the written description requirement of 35 U.S.C. § 112, first paragraph.

The Examiner acknowledges written descriptive support for those genes expressly and individually disclosed in the application-as-filed, fails to acknowledge any support being provided by the disclosure of the genus, or group, of non-essential genes found at page 5, lines 12-15, and emphasizes that failure by requesting citations to page and line numbers in the application-as-filed that support non-essential HSV genes not expressly and

individually identified. The Examiner is, thus, requiring express, literal support for the genes recited in amended claim 5, and that is an improper standard for written descriptive support. There is no requirement for ipsis verbis support; see Vas-Cath, Inc. v. Mahurkar, 19 USPQ.2d 1111, 1116 (Fed. Cir. 1991); MPEP § 2163 (3)(a).

At issue is whether one of skill in the art could reasonably conclude that the inventors had possession of the invention-as-claimed at the effective filing date. The application-as-filed literally discloses that the HSV may be further attenuated by deleting any of the genes found dispensable for viral replication in culture, and cites to the 1996 Roizman reference. (See page 5, lines 12-15.) In that Roizman reference, incorporated by reference into the application-as-filed, each of the 46 non-essential HSV genes is individually identified in Table 1. Thus, each of the 46 non-essential HSV genes was individually known in the art. On these facts, one of skill in the art would have understood that the disclosure in the application-as-filed that HSV could be further attenuated by deletion of one or more of the genes dispensable for viral replication in culture, was a disclosure that HSV could be further attenuated by deletion of one or more of the individually known non-essential HSV genes as identified in the 1996 Roizman reference. Stated alternatively, one of skill in the art would have had no difficulty in concluding that the inventors had possession of the invention defined by claims that recited uses of modified HSV further attenuated by deletion of one or more non-essential genes, regardless of whether those non-essential genes were collectively characterized as the "genes found dispensable for viral replication in culture" (synonym 1) or were individually identified as known members of the complete group of non-essential genes (synonym 2).

For the foregoing reasons, Applicants submit that, as a matter of law, there is no proper basis for rejecting any of claims 1-4 under 35 U.S.C. § 112, first paragraph, for asserted lack of written descriptive support and the rejection of those claims should be withdrawn. Further, Applicants submit that the rejection of claim 5 under § 112, first paragraph, for asserted lack of written descriptive support has been overcome and should be withdrawn.

C. The rejection of claims 1-14 and 16 for lack of enablement should be withdrawn

The Examiner rejected claims 1-14 and 16 under 35 U.S.C. § 112, first paragraph, for asserted lack of enablement in embracing methods of administration other than direct injection of tumors. In supporting remarks, the Examiner acknowledged that direct injection of a modified HSV expressing one $\gamma_1$34.5 gene into a tumor was enabled, but asserted that the specification does not reasonably provide enablement for treatment by any route of administration. The Examiner then turned to a consideration of the Wands factors, arguing that while the invention did not involve gene therapy *per se*, it did involve viral oncotherapy and, for that reason, delivery of therapeutic nucleic acids as a whole was relevant. In response, Applicants traverse and continue to maintain that a focus on gene therapy, or delivery of therapeutic nucleic acids, does not provide a useful framework for assessing he enablement of the pending claims.

1. The Wands factors

a. The nature of the invention.

The invention involves a therapeutic method for treating tumors that involves administration of a modified Herpes Simplex Virus that is selectively cytotoxic to dividing tumor cells. The invention does not involve gene therapy and does not fall into the realm of gene therapy. Moreover, the invention is not fairly characterized as the delivery of therapeutic nucleic acids insofar as the broadest claim of record is drawn to therapeutic uses of a modified form of a particular type of virus, and not any therapeutic nucleic acid. The claimed methods do not involve a modification of the genetic complement of the host cell, which is the realm of gene therapy and, more generally, the delivery of therapeutic nucleic acids. The methods as claimed do not insert, by addition or substitution, any gene or therapeutic nucleic acid into the host cell genome. The methods as claimed also do not require the engineered expression of a gene or therapeutic nucleic acid, unlike gene therapies and treatments based on the delivery of therapeutic nucleic acids. The claimed subject matter is drawn to viral therapies for tumors, and Applicants request that the examination focus on the merits of that subject matter.

The nature of the invention is the use of the well-known property of cytotoxic viruses such as HSV to kill cells. That property of viruses in general, and HSV more particularly, is known in the art. Moreover, biological mutants exhibiting altered properties, such as the modified HSV of the invention exhibiting selective cytotoxicity, are not uncommon to the geneticists and medical healthcare providers of skill in the art. Accordingly, the nature of the invention is the use of mutants to exploit the phenotypic variation of those mutants, an area that has received considerable attention for a number of years. The nature of the invention, therefore, is not unfamiliar to those of skill in the art and does not imply or establish that the claimed subject matter behaves unpredictably. In the Office Action, the Examiner confines his remarks regarding the nature of the invention to an assertion that the field of delivering therapeutic nucleic acids is relevant to the claims, a position that has been refuted above. Of equal importance, the Examiner has not challenged Applicants' assertion that the nature of the invention is not unpredictable, a factor favoring a conclusion that the pending claims are enabled throughout their full scopes.

b. State of the art and predictability.

The Examiner's focus remains misplaced in asserting that "the relevant art considered delivery of therapeutic nucleic acid, as a whole, to be extremely unpredictable." Office Action at page 5. In the previous Office Action at page 5, the Examiner asserted that "the relevant art considered gene therapy, as a whole, to be extremely unpredictable." Substituting one term, "delivery of therapeutic nucleic acid," for another term, "gene therapy," does not remedy any of the flaws in the Examiner's position that were established in Applicants' prior response. Applicants respectfully request a substantive reconsideration of the enablement rejection.

The claimed subject matter is drawn to methods of treating tumors using modified viruses, i.e., modified HSV. That is not a form of gene therapy, nor is it fairly characterized as merely a form of delivering a therapeutic nucleic acid, which the Examiner uses interchangeably with gene therapy (compare the outstanding Office Action and the previous Office Action). Delivering therapeutic nucleic acids (or gene therapy) must overcome delivery challenges not present in viral therapies in that delivering therapeutic

nucleic acids (or gene therapy) must deliver the nucleic acid (e.g., gene) to each cell in need of treatment. In contrast, the capacity of viruses to multiply and spread by infection reduces, if not entirely eliminates, that challenge. In addition, the modified HSV used in the claimed methods do not require the delivery and expression of a non-HSV therapeutic nucleic acid (e.g., gene) to be therapeutically effective, in contrast to the requirements of nucleic acid-based, or gene therapy-based, therapies. Rather, the claimed methods rely on the ability of HSV to infect and kill cells, with the modification of HSV shaping those natural properties to provide for selective cytotoxicity towards dividing cells such as tumor cells.

In addressing the state of the art and predictability thereof, the Examiner continued to rely on the same set of references, which will be addressed in the order presented in the Office Action. Verma et al. (1997) was cited for its recognition that gene delivery via viral vectors must overcome the challenge of an active immune system. Verma, however, was relied upon for its disclosure of a perceived general problem with the delivery of therapeutic viruses, that problem being "an immune system to fight off the virus." Office Action at page 5, citing Verma at page 293, column 3, paragraph 1. The Examiner has not asserted that Verma disclosed that an active immune system posed a problematic challenge to herpes simplex virus, however.

Any such assertion, moreover, would be contradicted by publications establishing that herpes simplex virus is able to infect human patients with active immune systems, including human patients that are HSV positive and have anti-HSV antibodies as a consequence. See, e.g., Kemeny et al., Ann. Oncol. Suppl. 216:ii283 (2005) and Fong et al., Amer. Soc. Clin. Oncol. Ann. Mtg., Abstract No. 27 (2002), both attached as Exhibit A hereto. Kemeny discloses delivery of HSV NV1020, a modified HSV expressing a single $\gamma_1$34.5 gene, by intrahepatic arterial infusion into human patients having colorectal adenocarcinomas that had metastasized to the liver and were refractory to first-line chemotherapeutics. Median survival time of 24 months was reported, with a maximum survival, to date, of 37 months. Earlier, Fong et al. reported for the same study that the virus was found in tumor tissue but not in normal liver and resulted in radiographically stable tumors with decreased CEA, indicative of efficacious treatment. In view of Kemeny and Fong, the extension of Vermi's generalized statements to the specific context of the

therapeutic delivery of modified herpes simplex viruses is unsupported and unwarranted speculation.

Chambers et al. was cited by the Examiner as teaching that the greater survival benefit of glioma-bearing mice exposed to HSV R4009 (stop codons in both copies of $\gamma_1$34.5) versus HSV R3616 (deletion of both copies of $\gamma_1$34.5) was perhaps attributable to the low level of $\gamma_1$34.5 read-through expression in R4009 versus R3616. As a first point, Applicants point out that the Examiner's focus is misplaced in considering the cause of any "greater" survival benefit. Even if such benefit were greater with one $\gamma_1$34.5-deficient HSV versus another, Chambers et al. does not disclose or suggest that a $\gamma_1$34.5-deficient HSV would provide no benefit. Thus, Chambers et al. confirms the predictability of a benefit from treating gliomas using either of two $\gamma_1$34.5-deficient HSV. In addition, the disclosure in Chambers et al. addressing HSV R4009 and HSV R3616, upon which the Examiner has relied, relates to HSV that have both copies of $\gamma_1$34.5 mutated. The claims are drawn to HSV having one expressible $\gamma_1$34.5 gene. Because both HSV R4009 and HSV R3616 have had both $\gamma_1$34.5 genes similarly mutated, these mutant HSVs must either express ICP34.5 from each $\gamma_1$34.5 gene or from neither gene, but not from just one $\gamma_1$34.5 gene. Thus, Chambers et al. does not provide guidance with respect to the predictability of the behavior of HSV having one expressible $\gamma_1$34.5 gene and the level of therapeutic benefit provided by HSV according to the claims is not a relevant measure of predictability in any event.

The Examiner's continued reliance on Crystal et al. is wholly misplaced. The Examiner continues to quote Crystal's assertion that "humans are not simply large mice," an obvious statement that does not advance the enablement inquiry because Crystal neither discloses nor suggests anything about therapeutic herpes simplex viruses. Crystal is a straightforward gene therapy reference addressing human gene transfer. See, e.g., the title, the abstract and the first sentence of the introduction. Crystal defines gene transfer in the second sentence of the introduction: "Essentially, gene transfer involves the delivery, to target cells, of an expression cassette made up of one or more genes and the sequences controlling their expression." None of the pending claims recites any "expression cassette" because the claimed subject matter is not drawn to gene transfer, gene therapy or the delivery of a therapeutic nucleic acid. As disclosed and claimed, the claimed subject matter is drawn

to therapeutic uses of modified herpes simplex viruses. Elsewhere in Crystal, vectors suitable for gene transfer are disclosed. Crystal expressly identifies the following: "The vector systems for which data are available from clinical trials (retroviruses, adenoviruses, and plasmid-liposome complexes) transfer expression cassettes . . . ." Page 404. Nowhere in Crystal is there a disclosure or suggestion of using HSV, even for gene transfer. Thus, any problem in relying on mouse models for gene transfer that does not even suggest the use of HSV cannot provide any guidance on whether mouse model data is useful in assessing methods of administering modified HSV to reduce tumor mass. More generally, the complete irrelevance of Crystal to the claimed subject matter means that Crystal cannot be informative on the state of the art for those claims or the predictability of that art.

Gura et al. has been relied upon for disclosing that animals apparently do not handle drugs the same way as humans in a quote relating to the testing of drugs by pharmaceutical companies and for asserting that drugs that appeared to be effective in xenograft models worked poorly in humans. Gura, however, is also completely irrelevant to the claimed subject matter. Gura is a publication addressing problems with systems for identifying new anti-cancer drugs. See, e.g., the title. The "drugs" addressed in Gura are chemical drugs, not viruses of any kind. In fact, there is not a single reference or suggestion to any virus in Gura, let alone to HSV. At page 1041, columns 1-2, bridging paragraph, Gura states that "some chemicals might have cancer-fighting effects. That evidence encouraged many chemists to explore the anti-cancer potential of similar agents . . . ." Chemists are not virologists. Consistently, at page 1042, first column, second paragraph, Gura states that "[o]ver the last 7 years, the panel [of human tumor cell lines] has been used to screen almost 63,000 compounds . . . ." Clearly, Gura is not referring to potentially oncolytic viruses. In the third column on that same page, last paragraph, Gura also refers to "drug developers" in its concluding sentence. Virologists, including clinical virologists, are not referred to as "drug developers." Gura's disclosures, upon which the Examiner continues to rely, are thus understood as completely uninformative on the issue of whether animal models of modified HSV oncotherapy are predictive of efficacy in patients. The Kemeny and Fong abstracts attached as Exhibit A establish that the positive results of HSV modified to have one expressed $\gamma_1$34.5 gene in treating human xenografts is positively correlated with, and thus predictive of, beneficial treatment of tumors in humans.

Kerbel et al. is also not helpful in establishing the state of the art, and its predictability, when that art is defined by the claimed subject matter. Kerbel, like Gura, relates to anti-cancer drugs that are not defined as oncolytic viruses. The Examiner cites Kerbel as support for the identification of three problems in relying on the mouse xenograft model. First, the maximum tolerated dose of the candidate may be greater in mice than in humans. HSV, including the modified HSV disclosed in the present application, has not been shown to be less oncolytic towards human xenografts in mice versus tumor cells in humans. Thus, this first problem establishes that Kerbel is addressing non-viral "drugs" that are uninformative on the issue of the enablement of the pending claims. Kerbel's second problem, that the faster growing xenograft tumors can show an exaggerated response to anti-cancer drugs relative to human tumors, is also uninformative. Kerbel has not even asserted that the general category of anti-cancer drugs is ineffective against human tumors. The fact that a response is "exaggerated" means that the baseline or reference response is also positive, i.e., therapeutically beneficial because a positive response can only be exaggerated in comparison to another positive response, not to a negative response. The magnitude of that therapeutic benefit does not change whether or not the claimed subject matter is efficacious and is not useful in addressing the issue of whether the claims are enabled. The third problem according to Kerbel is that the primary xenograft tumors are not representative of human metastasized tumors. Even focusing on the anti-cancer chemicals addressed by Kerbel, however, the fact that the mouse xenograft model is not suited to be predictive of both primary human tumors and metastasized human tumors does not mean that the model is not predictive of therapeutic efficacy in humans, e.g., in the context of treating primary tumors. Thus, Kerbel does not provide any support for the Examiner's assertion that the relevant state of the art is unpredictable and the reference is not informative on the broader issue of the enablement of the claims.

The Examiner also continues to rely on Muldoon for the proposition that not all routes of administration of the modified HSV are available to treat all tumors. In particular, the Examiner reiterates that "systemic administration of the HSV . . . would have no efficacy against glioblastoma, wherein the blood-brain barrier restricts entry of 120 nm HSV particles into the brain," citing Muldoon. Office Action at page 7; emphasis in the Office Action. Muldoon, however, stands for precisely the opposite proposition. That

reference discloses direct injection of either HSV or adenoviral gene therapy vectors into the brains of rats, and compares that mode of administration to the successful systemic intra-arterial delivery to the brain of each of the viral vectors, in conjunction with mannitol-induced hyperosmotic shock to permeabilize the blood-brain barrier. Thus, Muldoon supports the position that even for glioblastomas and other brain tumors, modified HSV may be administered by systemic delivery. Beyond establishing the actual disclosure in Muldoon, moreover, Applicants continue to maintain that one of ordinary skill in the art, faced with a known unavailability of one route of administration for treating one type of tumor, would simply use that information to choose a more appropriate route, and that fact does not diminish the scope of enablement. Muldoon, even if it did stand for the proposition that systemic delivery of modified HSV was foreclosed for the treatment of brain tumors, does not support the argument that the scope of enablement is not commensurate with the scope of any of the pending claims.

Having addressed each of the references upon which the Examiner has maintained reliance, it is apparent that none of those references is informative in establishing the state of the art relevant to the claimed subject matter and none of those references supports the position that the art is unpredictable. Accordingly, Applicants position with respect to the developed state of the art and the predictability thereof stands unopposed.

c. Claim breadth and direction/guidance.

In subjectively characterizing the claims as "very broad," the Examiner focuses on the route of administration, which is not an essential limitation of the claimed subject matter. The inventors' contributions, as defined in the pending claims, are methods of reducing tumor mass in patients using HSV having a particular modification, i.e., a modification in an inverted repeat region such that only one $\gamma_1$34.5 gene is expressed. The route of administration is not essential to the claimed methods because any route of administration known to be suitable for administration of the modified virus to treat the particular tumor may be used. This situation is analogous to a claim for a pharmaceutical composition comprising a polynucleotide having a unique sequence. A claim to such a composition need not, and would not, recite a particular excipient unless that excipient were

essential to the function of the composition. A claim to such a composition is not "very broad" simply because it is not limited to a particular, and non-essential, excipient. The present claims, in fact, are precisely tailored to the invention disclosed in the pending application and are not overbroad.

In addressing the guidance factor, the Examiner relies on Muldoon in asserting that intramuscular administration of the modified virus would be ineffective in treating glioblastoma because of the blood-brain barrier. As noted above, however, Muldoon stands for precisely the opposite proposition, i.e., Muldoon discloses that systemic administration of modified HSV, whether via intravenous or intramuscular injection or the like, would be effective in treating glioblastoma because of the known availability of mannitol-induced hyperosmotic shock leading to alterations in the permeability of the blood-brain barrier that render it permeable to HSV. Moreover, one of skill, aware of the blood-brain barrier, could alternatively choose to would avoid routes of administration incompatible with delivery of the therapeutic to the tumor to be treated. Under the law, inoperative embodiments that cannot even be identified without experimentation do not inevitably lead to a conclusion that claims are not enabled. If one of skill in the art already knows that not all routes of administration are suitable for treating a particular tumor, there can be no doubt that a specification need not reiterate such information in order to provide an enabling disclosure.

The Examiner also argues that there is a lack of reference between the in vivo nude mouse model data [and] results which skilled artisan would expect in humans. In particular, the Examiner asserts an absence of guidance as to how to modify the treatment in shifting from the immunocompromised mouse to an immunocompetent patient. HSV itself, however, has demonstrated a capacity to avoid eradication by the host immune system, and one of skill in the art has been aware of that fact for some time. Moreover, Kemeny and Fong, attached as Exhibit A, establish that modified HSV are therapeutically effective upon administration to tumor-bearing humans that are not immunocompromised. Thus, there is no reasonable basis for believing that HSV, long-known for successfully infecting immunocompetent hosts, would be rendered fatally immunosensitive simply because delivery was directed by man to treat a tumor.

The Examiner also maintains that "empirical experimentation would be required to determine an effective amount to treat" various tumors. Office Action at page 8. Optimization of dosage is a routine matter for health professionals that is well within the skill of those of ordinary skill in the art. Such experimentation involves routine procedures and, while the activities may involve "empirical experimentation," that experimentation is not, and never has been, regarded as undue. The issue of optimization of dosage attends every therapeutic method involving delivery of a therapeutic and the inevitable dosage optimizations attending practice of all of those methods, including the many patented methods, involves routine, not undue, experimentation.

d. The quantity of experimentation.

The Examiner asserts that the "specification lacks sufficient guidance to surmount the technical difficulties recognized in the art," and asserts that "the prior art also lacks solutions to overcome the considerable list of obstacles recognized in the field," thus requiring trial-and-error experimentation to overcome the obstacles Office Action at page 9. Further, the Examiner asserts that "as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art." *Id.* The Examiner fails to identify any of these problems or obstacles, however, and the conclusion that undue experimentation would be required is, thus, unsupported. Even if these problems or obstacles were identified in passages of the Office Action prior to page 9, Applicants have addressed each of the Examiner's positions without recognizing problems or obstacles requiring anything more than routine, and certainly not undue, experimentation. Therefore, Applicants respectfully submit that, at most, a minimal quantity of expected experimentation of a routine nature would be required and this factor favors a conclusion that the claimed subject matters are enabled by the application-as-filed.

For all of the foregoing reasons, Applicants submit that a consideration of the Wands factors in the present matter leads to a conclusion that each of claims 1-14 and 16 is enabled throughout its full scope by the application-as-filed. A *prima facie* basis for rejecting

any of those claims under 35 U.S.C. § 112, first paragraph, for lack of enablement has not been established and, accordingly, the rejection should be withdrawn.

D. The rejection of claims as anticipated by either Advani (1997) or Advani (1998) should be withdrawn

In the Office Action, the Examiner asserts that the claims are drawn to methods for reducing tumor mass by administering a modified HSV having only one active $\gamma_1$34.5 gene, with those claims explicitly encompassing the administration of HSV R7020 and treating CNS tumors. The Examiner characterizes Advani (1997), a published abstract, as disclosing the administration of HSV R7020 to athymic mice bearing a human glioma xenograft. Further, Advani (1997) is characterized as stating that "radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas." Office Action at page 10 (emphasis in Office Action).

The Examiner relied on Advani (1998) as teaching the same data as Advani (1997), but with more detail. The Examiner asserted that Advani (1998) taught "a number of different experiments" wherein HSV R3616, an HSV not modified in accordance with the present invention, was directly administered to glioma xenografts by itself or in combination with other agents, and tumor volumes were measured at different time points. Office Action at page 11. For all of these experiments concerning HSV R3616, the Examiner cited Figs. 1 and 2 of Advani (1998), which addressed data relating to HSV R3616, but not any data relating to HSV R7020. The Examiner then quoted Advani (1998) as stating that "'the experiment was repeated with R7020, another genetically engineered attenuated virus,' (see p. 161, bottom of second column), indicating that the R7020 was also injected into glioma xenografts in a nude mouse model and tumor volume was measured at certain time points." *Id.*

Applicants disagree with the Examiner's characterization of Advani (1998). The passage at the bottom of page 161, second column, of Advani (1998), upon which the Examiner relied, recites that, "[t]o determine whether the effects of irradiation were specific for $\gamma_1$34.5 R3616, the experiment was repeated with R7020, another genetically engineered

attenuated virus." That statement, referring to a single experiment, is found in the second paragraph of a section of the paper titled "*[v]iral replication in irradiated tumor cells.*" Advani (1998) at page 161, second column. In the first paragraph of that section, Advani (1998) describes an experiment to measure the replication of R3616 by exposing tumor xenografts to either the R3616 virus alone, or to the virus and to ionizing radiation. It was to this single experiment that the quoted statement (upon which the Examiner relied) in the next paragraph of Advani (1998) was making reference. Consistently, the results of the experiment with R7020 were provided in Figure 3 of Advani (1998), a figure that appears to be identical to the sole figure provided in Advani (1997). Thus, the experiment involving R7020 that was described in Advani (1998) is the same type of experiment, if not the very same experiment, as described in Advani (1997). That experiment involved the delivery of R7020 to a tumor xenograft, followed by tumor excision and destruction to measure viral titer and thereby assess viral repliction. Advani (1998) does not disclose, suggest or imply that any other experiment was performed with R7020, including any experiment in which tumor volume was measured. Thus, while Advani (1998) is a paper that provides more detail than the abstract of Advani (1997), that detail concerns the behavior of HSV R3616, an HSV not within the scope of the modified HSVs described in the present application.

Applicants continue to vigorously maintain that Advani (1998) neither anticipates nor renders obvious the subject matter of any of the rejected claims. Notwithstanding that position, however, Applicants acknowledge that Advani (1998) is a publication by, inter alia, the named inventors. Accordingly, Applicants attach as Exhibit B a Declaration of Ralph Weichselbaum that establishes that any disclosures in Advani (1998) that may be relevant to the claimed subject matter were the inventors' own disclosures and, hence, are not available against the pending claims.

In response to Applicants' prior argument that Advani (1997) (and Advani (1998)) fail to teach a reduction in tumor mass resulting from administration of HSV R7020, the Examiner asserts that such a reduction would have been inherent in the methods disclosed by Advani (1997) (and Advani (1998)). Applicants respectfully disagree.

Under the law, the doctrine of inherency provides that a reference that does not expressly disclose each limitation of a claim may nevertheless anticipate the claimed subject matter if the missing subject matter is inherently disclosed. M.P.E.P. § 2112 (IV). For subject matter to be inherently disclosed, it must necessarily be found in the prior art disclosure. *Id.* Mere probabilities are insufficient, and the requirement to optimize conditions for that subject matter to be present means that the undisclosed subject matter is not inherently present. *See In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993), *In re Oelrich*, 212 U.S.P.Q. 323,326 (C.C.P.A. 1981). Applicants have consistently noted that Advani (1997) (and Advani (1998)) does not disclose tumor mass or volume reduction by HSVs expressing a single $\gamma_1$34.5 gene, even in xenograft mouse models of gliomas. Applicants disagree with the Examiner's position that Advani (1997) (or Advani (1998)) inherently discloses such a tumor mass reduction using HSV R7020. Advani (1997) (and Advani (1998)) reported measurements of R7020 viral titers and R7020 viral distributions in tumor xenografts upon tumor excision and destruction. Advani (1997) (and Advani (1998)) did not test any effect on tumor mass or volume attributable to R7020 and, consistently, did not disclose experiments to find a dose of R7020 that would result in tumor mass reduction. Moreover, even if dosage is recognized as being routinely determined in the art of viral oncotherapy, Advani (1997) (and Advani (1998)) addressed the research issue of the effect of ionizing radiation on HSV R7020 replication in a tumor xenograft, not the effect of HSV R7020 on tumor mass or volume. Thus, Advani (1997) (and Advani (1998)) did not disclose or suggest even the routine experimentation required to arrive at a dose that would result in tumor mass or volume reduction.

One of skill in the art would recognize that there are limits to dosages of a modified HSV, such as R7020, that result in tumor mass reduction. Therefore, not every dosage of HSV R7020 would be expected to lead to tumor mass reduction. For that reason, tumor mass reduction does not inhere in the administration of R7020, alone or in conjunction with ionizing radiation, to an athymic nude mouse bearing a glioma tumor xenograft. Accordingly, under the law, Advani (1997) (and Advani (1998)) does not inherently disclose tumor mass or volume reduction resulting from administration of HSV R7020. Further, Advani (1997) (and Advani (1998)) does not expressly disclose tumor mass or volume reduction resulting from administration of a modified HSV (e.g., R7020), and there is no

disagreement regarding that fact. Therefore, Advani (1997) (and Advani (1998)) fails to disclose, expressly or inherently, each limitation of any of the pending claims. A *prima facie* basis for anticipation of the claimed subject matter in view of Advani (1997) (or in view of Advani (1998)) has not been established and the rejection should be withdrawn.

E. The rejection of claims as obvious over either Advani (1997) or Advani (1998) in view of Carroll has been overcome

The Examiner relied on Advani (1997) and Advani (1998) for the disclosures characterized above in the context of addressing the rejection of claims for asserted lack of novelty in view of each of those references. The secondary reference, Carroll, was cited as disclosing the administration of a viral-based therapy to treat non-CNS tumors. In response, Applicants traverse.

To establish a *prima facie* basis for rejecting a claim as obvious over a combination of references, as here, the initial burden is on the Examiner to establish a motive to combine the references, to show a reasonable expectation of success in arriving at the claimed invention upon that combination, and to establish that each limitation of a rejected claim is disclosed or suggested by the combined references. Applicants respectfully submit that the Examiner has not met that initial burden.

The Examiner's reliance on Advani (1998) is misplaced for the dispositive reason that Advani (1998) is not available as a reference against any of the pending claims because any relevant disclosure is a disclosure of the inventors themselves, as established by the Declaration of Ralph Weichselbaum (Exhibit B). In addition, the Examiner's reliance on either Advani (1997) or Advani (1998) was misplaced because each of these references failed to inherently disclose the reduction of a tumor mass or volume by administering HSV R7020, a modified HSV expressing a single $\gamma_1$34.5 gene, as established above. The defect in Advani (1997) and Advani (1998) is not remedied by Carroll, and the Examiner has not contended otherwise. Thus, considering either Advani (1997) or Advani (1998) in combination with Carroll, each of the combinations of references fails to disclose or suggest each limitation of any of the rejected claims.

In addition to the failure of the combined references to disclose or suggest each limitation of any of the rejected claims, there is no proper motive or suggestion to combine either Advani (1997) and Carroll, or Advani (1998) and Carroll. Neither of the primary references, Advani (1997) and Advani (1998), has been shown to disclose or suggest a reduction in tumor mass or volume attributable to HSV R7020, a modified HSV in accordance with the invention. Consequently, the Examiner has not established that either of these primary references discloses or suggests a therapeutic method for treating a tumor using HSV R7020. In view of that failure, one of skill in the art would not be motivated to look to Carroll to adapt the Advani disclosure (either Advani (1997) or Advani (1998)) to treat a non-CNS tumor. Thus, the Examiner has not established a motive or suggestion to combine either Advani (1997) or Advani (1998) with Carroll.

In view of the failure to establish a motive or suggestion to combine the references and a failure to disclose or suggest each limitation of any of the rejected claims even if those references are combined, there can be no reasonable expectation of successfully arriving at the invention in view of either Advani (1997) or Advani (1998) when considered in combination with Carroll. In addition to the foregoing reasons, the unavailability of Advani (1998) against any of the pending claims provides an additional dispositive reason that Advani (1998), alone or in combination with Carroll, does not prejudice the novelty and non-obviousness of the claimed subject matter.

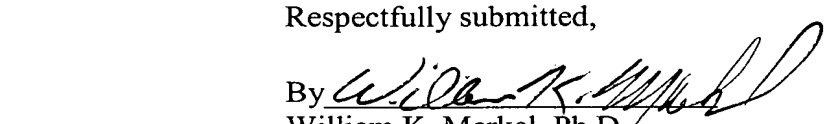
For the foregoing reasons, Applicants submit that the Examiner has not satisfied any of the three requirements for establishing a *prima facie* basis for rejecting any of the claims as obvious under 35 U.S.C. § 103(a) over either Advani (1997) or Advani (1998) when either reference is considered in view of Carroll. In addition, Advani (1998) is not properly available as a reference against any of the rejected claims. Accordingly, the rejection of claims 1-14 and 16 has been overcome and should be withdrawn.

F. Conclusion

For all of the foregoing reasons, Applicants submit that all outstanding rejections and objections have been overcome and pending claims 1-14 and 16 are in condition for allowance. An early notice thereof is respectfully solicited.

Dated: June 26, 2006

Respectfully submitted,

By 

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Results: Three hundreds and seventeen patients were eligible for our analysis. Median age at diagnosis was 64 years (range 26–88). Male/female ratio was 184/133; 285 patients (89.9%) were diagnosed with adenocarcinoma, whilst 32/317 (10.1%) with mucinous adenocarcinoma. Neoadjuvant treatments performed were as follows: radiotherapy alone in 74/317 patients (23.3%), radiotherapy plus chemotherapy 242/317 patients (76.7%). In order to determine the importance of downstaging after neoadjuvant treatment we identified a novel score, calculated by the sum of numbers obtained giving a negative or positive point respectively to each degree of increase or decrease from clinical to pathological T and N status. At univariate and multivariate analysis including the following factors: age, sex, type of neadjuvant treatment (radiotherapy vs chemo-radiotherapy), histotype (mucinous vs non-mucinous), was performed. An higher score was observed in males ($p = 0.02$) and in those patiets receiving neoadjuvant chemo-radiotherapy ($p = 0.0001$). A worse time to progression was observed in patients with an higher score ($p = 0.04$).

Conclusions: Our results suggest that a novel score, calculated from preoperative and pathological tumor and lymph-nodal status could represent an important parameter able to predict the outcome in patients receiving neoadjuvant treatment for rectal cancer. The score, that quantifies the downstaging of the tumor, could be useful in order to select patients to receive adjuvant chemotherapy after neoadjuvant treatment and surgery for locally advanced rectal cancer.

47O Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first line treatment of metastatic colorectal carcinoma (MCRC): results of a safety and efficacy analysis

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Background: In a previous phase III study the FUFOX regimen has shown superior response rates than Mayo Clinic protocol in patients with ACRC (Grothey, ASCO 2002). The combination of capecitabine (CAP) and oxaliplatin (OX) has demonstrated good efficacy and safety results in recent phase II studies. In August 2002 we initiated a phase III trial to compare FUFOX and CAPOX as 1st line therapy in patients with ACRC. Here, we present the results of the planned safety and efficacy analysis.

Patients and methods: From August 2002 to August 2004 476 patients [pts = 298:176; median age 65 (range 32–86)] were randomized to receive either FUFOX (233 pts. arm A: 5-fluorouracil 2000 mg/m^2 24 h infusion, folinic acid 500 mg/m^2, oxaliplatin 50 mg/m^2 d1,8,15,22; q5 wks) or CAPOX (241 pts arm B: capecitabine 1000 mg/m^2 bid d1–14, oxaliplatin 70 mg/m^2 d1 and 8; q3 wks). All patients had measurable metastatic disease, ECOG performance status 0–2, normal renal and hepatic function.

Results: To date 2396 treatment cycles (948 FUFOX, 1448 CAPOX) are available for toxicity (median no. of cycles/ patient: arm A: 4, range 1–21; arm B: 6, range 1–21. Both regimens showed comparable toxicity profiles with more HFS (hand–foot syndrome) in the CAPOX arm. Median follow-time was 35 weeks in both arms. Based on 278 events currently observed, median prgression free survival (PFS: primary study endpoint) was 35 weeks in the FUFOX arm and 30 weeks in the CAPOX arm, respectively (HR: 1.22 (90% CI: 1–1.49; $p = 0.1$). Secondary efficacy parameters are detailed in Table 2.

Conclusions: In this phase III study CAPOX shows for the first time comparable efficacy and toxicity profiles compared to the FUFOX regimen in patients chemonaive ACRC.

Table 1. Grade 3/4 toxicity

Toxicity (Grade), %	3 FUFOX/CAPOX	4 FUFOX/CAPOX
Asthea	11/11	3/4
Enteritis	2/0	1/1
Neuropathy	23/19	4/4
HFS/Foot (Grade 2/3)	4/9	0/1
Leukopenia	3/3	4/3
Neutropenia	3/3	4/3
Thrombopenia	1/2	0/0

Table 2. Response rates

Response rates	CAPOX ($n = 197$)	FUFOX ($n = 183$)
CR	3	5
PR	44	41
SD	28	23
PD	25	30

48O Results of a phase I, dose-escalating study of the safety, tolerability and anti-tumor activity of a single injection of a genetically engineered herpes simplex virus, nv1020, in subjects with hepatic colorectal metastases

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Background: Oncolytic Herpes simplex virus (oHSV) therapy is a promising new strategy to treat tumors due to the creation of virus variants that can selectively replicate, spread *in situ*, and lyse malignant cells while sparing normal tissue. Oncolytic herpes simplex viruses have also demonstrated efficacy against chemotherapy-resistant cancers in preclinical studies.

Objective: To investigate safety, tolerability and anti-tumor activity of NV1020, a replication-competent, attenuated, genetically engineered herpes simplex virus type-1, in patients with colorectal adenocarcinoma metastatic to the liver refractory to first line chemotherapy.

Design: Phase I, open-label, dose-escalating study of a single 10 minute intrahepatic arterial infusion (IHA) of NV1020 in four cohorts ($n = 3$/cohort), receiving escalating doses of 3×10^6, 1×10^7, 3×107, 1×10^8 plaque-forming units (pfu), followed by regional chemotherapy.

Patients: 12 patients in 4 cohorts participated, 9 males, 3 females.

Results: Adverse events were either mild or moderate in severity, and self-limiting. 3 self-limiting serious adverse events experienced by 3 patients were considered possibly or probably related to NV1020. None resulted in death. These events comprised a transient isolated elevation of GGT (Grade 4) 12 hours after NV1020 infusion (1×10^8 pfu NV1020) in a patient with a history of hepatitis, a case of gastroenteritis, and a case of mild leukocytosis considered due to a respiratory infection. GGT levels normalized at 24 hours after NV1020 infusion. Overall, there was no evidence of disseminated herpes infection. Viral presence was detected in only one saliva sample and two serum samples from one asymptomatic patient in the highest dose cohort. In the 28 days prior to start of chemotherapy, a tumor regression (39% area reduction) was noted in one patient while another patient had 20% tumor reduction. After start of chemotherapy, all patients exhibited a radiographic response, and median CEA decline was 23% at month 3. As of January 2005, overall median survival time of all 12 patients was 24 months with maximal survival so far of 37 months. One patient is still alive at 30 months post therapy. These data are very promising for patients who had already failed 1st-line therapy.

49P NAT2, meat consumption and colorectal cancer incidence: an ecological study among 27 countries

Simona Ognjanovic, Jennifer F. Yamamoto, Loic Le Marchand, Gertraud Maskarinec

Cancer Research Center, Epidemiology, Honolulu, HI, USA

Aim: Inter-individual differences in N-acetyltransferase (NAT) activity and in the resulting ability to bioactivate heterocyclic amines from cooked meats, is determined by two polymorphic genes (NAT1 and NAT2).

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Meeting: 2002 ASCO Annual Meeting
Category: Biologic and Targeted Therapies
SubCategory: Gene Therapies and Antisense Strategies

Bookmark

Phase 1 study of a replication-competent herpes simplex oncolytic virus for treatment of hepatic colorectal metastases

Abstract No: 27

Author(s): Yuman Fong, Nancy Kemeny, William Jarnagin, Steve Stanziale, Brenda Guilfoyle, Niraj Gusani, John Joe, Leslie Blumgart, Fred Lakeman, Karen Gammon, Joanna Perterkin, Brian Horsburgh, Frank Tufaro, Memorial Sloan-Kettering, New York, NY; University of Alabama, Birmingham, AL; MediGene Inc, San Diego, CA.

Abstract: Background: Genetically engineered replication competent herpes simplex viruses (HSV) have shown promise in tumor specific infection, replication, and lysis in pre-clinical models. The current study represents the first attempt to delivery such an HSV (NV1020) into the bloodstream for the treatment of human disease. Methods: NV1020 is a genetically engineered HSV with a deletion in UL24 and all genes contained in one copy of the inverted repeats to decrease virulence in non-malignant tissues. This virus was delivered into the hepatic artery of patients with hepatic metastatic colorectal cancer via percutaneous catheter in a phase 1 trial. Three days later during surgical exploration for hepatic infusion pump placement, tumors and non-malignant liver were biopsied. Patients were observed for 28 days before starting regional chemotherapy. Preliminary Results: The first nine patients have been treated at three respective dose levels (1.3×10^6, 10^7, 1.3×10^7 plaque forming units (pfu)). No dose-limiting toxicities have been observed. The only adverse effects possibly attributable to virus infusion were: fever (7/9), nausea (3/9), and headache (2/9). NV1020 DNA PCR, but not infectious virus, was detectable in the hepatic venous effluent in 2 patients. NV1020 has been detected in tumor tissue by immunohistochemistry but not in normal liver. Tumors were radiographically stable and all patients experienced a decrease in CEA during the 28-day period. ($370f120$ to $270f80$, $p<0.001$ by paired t-test). Conclusions: It appears that herpes simplex viruses can be safely delivered into the bloodstream. The MTD has not yet been reached but is above 1.3×10^7 pfu. The trial is on-going.

Associated Presentation(s):

1. **Phase 1 study of a replication-competent herpes simplex oncolytic virus for treatment of hepatic colorectal metastases**
   Event: 2002 ASCO Annual Meeting
   Presenter: Yuman Fong, MD
   Session: Biologic and Targeted Therapies
   (No presentation available)

Other Abstracts in this Sub-Category:

1. **A phase 1, dose-escalation trial of E1A gene transfer with chemotherapy for treatment of advanced ovarian cancer**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 69 First Author: David S Alberts

2. **A phase I dose-escalation pharmacokinetic and pharmacodynamic study of INGN 241 (Ad-mda7) in**

patients with advanced solid tumors
Meeting: 2002 ASCO Annual Meeting Abstract No: 87 First Author: C C Cunningham

3. **Adenovirus-IκBα-superrepressor confers sensitization to TRAIL-induced apoptosis in A549 cells by repressing NF-κB-dependent cIAP2 induction**
Meeting: 2002 ASCO Annual Meeting Abstract No: 1849 First Author: Kye Young Lee

4. **AdV-tk/valacyclovir gene therapy in combination with radiotherapy for prostate cancer: interim results of a phase I/II clinical trial**
Meeting: 2002 ASCO Annual Meeting Abstract No: 25 First Author: Laura K Aguilar

5. **cDNA microarray evaluation of non-Hodgkin's lymphoma cells reveals multiple changes in gene expression profiles induced by Bcl-2 antisense (Genasense™).**
Meeting: 2002 ASCO Annual Meeting Abstract No: 1905 First Author: Tiffanie J Powell

6. **Chemogene treatment consisting of recombinant adenoviral transfection of p16cDNA (SVN-22/3), vinorelbine and docetaxel eradicates chemoresistant aneuploid pancreatic adenosquamous Ca characterised by overexpression of K-Ras and hypermethylation of CpG islands of p16 (INK4A).**
Meeting: 2002 ASCO Annual Meeting Abstract No: 1927 First Author: Emmanuel Michailakis

7. **Consequences of combining chemotherapy and gene therapy**
Meeting: 2002 ASCO Annual Meeting Abstract No: 1890 First Author: G. A Hospers

8. **Enhanced adenoviral gene transfer in ovarian cancer**
Meeting: 2002 ASCO Annual Meeting Abstract No: 1930 First Author: Ingo B Runnebaum

9. **Expression of suicide genes increases the selective oncolytic effect of the vesicular stomatitis virus**
Meeting: 2002 ASCO Annual Meeting Abstract No: 90 First Author: Mercedes Porosnicu

10. **Inhibition of c-Kit receptor expression in malignant human neuroepithelial cells by RNA interference**
Meeting: 2002 ASCO Annual Meeting Abstract No: 1929 First Author: Carl T Henningson Jr.

Other Abstracts by Author: Yuman Fong

1. **Extensive hepatic resection does not correlate with toxicity following adjuvant chemotherapy**
Meeting: 2002 ASCO Annual Meeting Abstract No: 526 First Author: Amanda Hummer

2. **A phase I study of hepatic arterial infusion (HAI) of floxuridine (FUDR) and dexamethasone plus systemic (SYS) oxaliplatin and irinotecan or HAI plus SYS oxaliplatin and fluorouracil and leucovorin for unresectable hepatic metastases from colorectal cancer**
Meeting: 2002 ASCO Annual Meeting Abstract No: 559 First Author: Nancy Kemeny